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(19) (CA) **CANADIAN PATENT** (12)

(54) 1,4-Dihydropyridine Compounds Linked in the C-3 Position, Their Production and Their Medicinal Use

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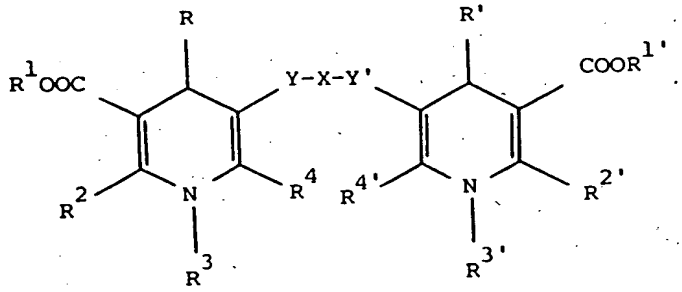
The present invention relates to certain new dimeric 1,4-dihydropyridine compounds which are linked to one another in the 3-position, to several processes for their preparation and to their use in medicaments having an influence on the circulation.

It is already known that certain 1,4-dihydropyridine derivatives have interesting pharmacological properties (see F. Bossert et al., Naturwissenschaften 58, 578 (1971) and DT-OS (German Published Specification) 2,117,571).

According to the present invention we provide compounds which are 1,4-dihydropyridines linked in the C-3 position, of the general formula



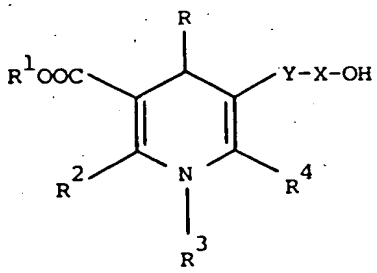
I

or a salt thereof, in which R and R' are identical or different and each represent a phenyl or naphthyl radical or a heterocyclic radical selected from thienyl, furyl, pyrryl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, quinolyl, isoquinolyl, indolyl, benzimidazolyl, quinazolyl, or quinoxalyl radical, the aryl or heterocyclic radical optionally carrying 1 or 2 identical or different substituents selected from phenyl, alkyl with 1 to 8 carbon atoms, cycloalkyl with 3 to 7 carbon atoms, alkenyl or alkinyl with in each case 2 to 6 carbon atoms, alkoxy, alkenoxy or alkinoxy with in each case up to 4 carbon atoms, an alkylene chain with 3 to 6 carbon atoms, dioxyalkylene with 1 or 2 carbon atoms, halogen, trifluoromethyl, trifluoromethoxy, difluoromethoxy, tetrafluoroethoxy, nitro, cyano, azido, hydroxyl, amino, mono- or di-alkylamino with in each case 1 to 4 carbon atoms per alkyl group, carboxyl, carbalkoxy with 2 to 4 carbon atoms,

carboxamido, sulphonamido and sulphonylalkyl or alkylmercapto with in each case 1 to 4 carbon atoms per alkyl radical; R^1 and $R^{1'}$ are identical or different and each represent a straight-chain, branched or cyclic, saturated or unsaturated hydrocarbon radical which has up to 8 carbon atoms and is optionally interrupted in the chain by 1 or 2 oxygen atoms and is optionally substituted by fluorine, chlorine, hydroxyl, phenyl, phenoxy, phenylthio or phenylsulphonyl, the phenyl radicals in turn optionally being substituted by 1 or 2 identical or different substituents selected from nitro, trifluoromethyl, cyano, fluorine, chlorine and alkyl and dialkylamino with in each case 1 to 4 carbon atoms in the alkyl radicals; R^2, $R^{2'}$, R^4 and $R^{4'}$ are identical or different and each represent a hydrogen atom or a straight-chain, branched or cyclic, saturated or unsaturated hydrocarbon radical which has up to 8 carbon atoms and is in turn optionally substituted by fluorine, chlorine, hydroxyl, phenyl, amino, alkylamino or cycloalkyl with up to 6 carbon atoms; R^3 and $R^{3'}$ are identical or different and each represent a hydrogen atom or a straight-chain or branched alkyl radical which has up to 8 carbon atoms and optionally is interrupted in the chain by an oxygen atom or is substituted by hydroxyl or halogen, or represent optionally substituted phenyl, benzyl or phenethyl radical; Y and Y' are in each case identical or different and each denote -COO-, -CONH-, -CO-, -COS- or $-SO_2-$ and X represents a bridge member which has at least one CH_2 group which is not bonded to the rings and at most 9 adjacent CH_2 as chain members, it being possible for the bridge member additionally to contain, in any desired sequence, 1 to 4 identical or different chain members selected from O, S, SO_2, CO, CS, NR^5, $C(R^6)_2$, $CR^6=CR^6$, C≡C, CH=N, phenylene, naphthylene, pyridylene and cycloalkylene or cycloalkenylene with in each case 3 to 7 carbon atoms, piperazinylene, piperidinylene, pyrrolidinylene and morpholinylene, wherein R^5 represents a hydrogen atom, a benzyl radical or an alkyl radical with 1 to 4 carbon atoms and R^6 represents a hydrogen atom, a benzyl or phenyl radical, a fluorine or

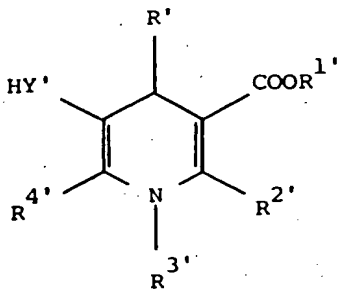
chlorine atom, an alkyl radical with 1 to 4 carbon atoms, a hydroxyl, trifluoromethyl, cyano, carboxyl or amino radical, an alkylamino radical with 1 to 4 carbon atoms in the alkyl radical or a carbalkoxy radical with 1 to 4 carbon atoms in the alkoxy radical, which process comprises:

(a) reacting a hydroxy-1,4-dihydropyridine derivative of the general formula



II

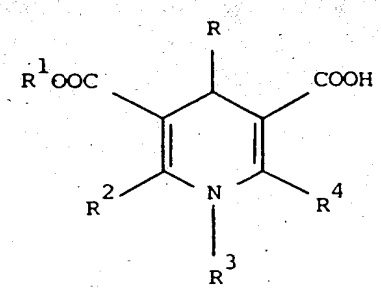
in which R, R^1, R^2, R^3, R^4, Y and X have the definitions given above, with an equivalent amount of a dihydropyridine-3-carboxylic acid derivative of the general formula



III

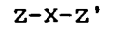
in which R', $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ and Y' have the definitions given above, but Y' does not represent a carbonyl group, in an inert organic solvent in the presence of water-binding agents at a temperature between 0°C and 180°C, water being split off, or

(b) reacting a 1,4-dihydropyridinecarboxylic acid of the general formula



IV

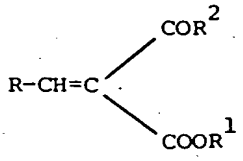
in which R, R^1, R^2, R^3 and R^4 have the definitions given above, is reacted with a bifunctional compound of the general formula



V

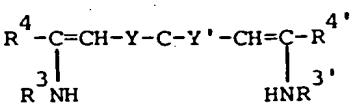
in which X has the definition given above and Z and Z' are in each case identical or different and represent a hydroxyl, mercapto or NHR^5 radical, wherein R^5 has the definition given above, in a molar ratio of about 2:1 in the presence of an inert organic solvent at a temperature between 0°C and 180°C, only a compound of the general formula I in which Y and Y' do not represent a carbonyl group being obtained by this variant, or

(c) reacting an ylidene-β-keto ester of the general formula



VI

R, R^1 and R^2 have the definitions given above, with an enaminocarboxylic acid ester of the general formula



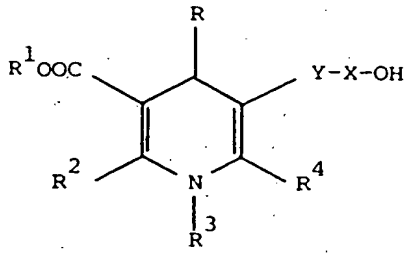
VII

in which R^3, $R^{3'}$, R^4, $R^{4'}$, Y and Y' have the same meanings as defined above, in a molar ratio of about 2:1 in the presence of an inert organic solvent at a temperature between 0°C and 180°C, and, if required, converting a compound of formula I into a pharmaceutically acceptable salt thereof.

According to the present invention we further provide a process for

the production of a compound of the invention, in which

(a) a hydroxy-1,4-dihydropyridine derivative of the general formula



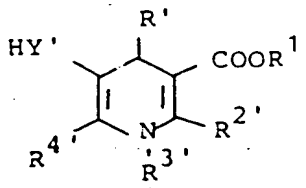
II

B

in which

R, R^1, R^2, R^3, R^4, Y and X have the abovementioned meanings,

is reacted with an equivalent amount of dihydropyridine-3-carboxylic acid derivative of the general formula



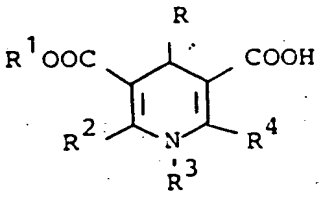
(III)

in which

R', $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ and Y' have the abovementioned meanings, but Y' does not represent a carbonyl group,

in an inert organic solvent in the presence of a water-binding agent at a temperature between 0°C and 180°C, water being split off, or

b) a 1,4-dihydropyridinecarboxylic acid of the general formula



(IV)

in which

R, R^1, R^2, R^3 and R^4 have the abovementioned meaning,

is reacted with a bifunctional compound of the general formula

$$Z\text{-}X\text{-}Z' \qquad (V)$$

in which

X has the abovementioned meaning and

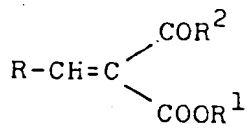
Z and Z' are in each case identical or different and represent hydroxyl, mercapto or a NHR^5 radical wherein

R^5 has the abovementioned meaning,

in a molar ratio of about 2:1 in the presence of an inert

organic solvent and, if appropriate, in the presence of a water-binding agent, at a temperature between 0°C and 180°C, only compounds of the general formula (I) in which Y and Y' do not represent a carbonyl group being obtained by this variant, or

c) an ylidene-β-keto ester of the general formula

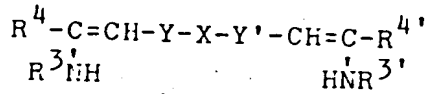


(VI)

in which

R, R^1 and R^2 have the abovementioned meanings,

is reacted with an enaminocarboxylic acid ester of the general formula



(VII)

in which

R^3, $R^{3'}$, R^4, $R^{4'}$, Y and Y' have the abovementioned meanings,

in a molar ratio of about 2:1 in the presence of an inert organic solvent at a temperature between 0°C and 180°C.

Preferably symmetric compounds, that is to say compounds in which in each case Y and Y', R^3 and $R^{3'}$ and R^4 and $R^{4'}$ are identical, are prepared by this process variant c). Symmetric compounds of the general formula (I) in which Y denotes a carbonyl group can also be prepared by this process variant c).

The dihydropyridines of the general formula (I) according to the invention have valuable pharmacological properties. By virtue of their circulation-influencing action, they can be used as antihypertensive agents, as vasodilators, as cerebral therapeutic agents and as coronary therapeutic agents. Surprisingly, they exhibit particularly long-lasting actions and are thus to

be regarded as an enrichment of pharmacy.

Compounds of the general formula I according to the invention which are of particular interest are those in which R and R' are identical or different and each represent a phenyl radical or a thienyl, furyl, naphthyl, or pyridyl radical, the phenyl radical optionally being substituted by one or two identical or different substituents selected from nitro, cyano, azido, halogen, trifluoromethyl, hydroxyl, amino and alkyl, alkoxy, alkylamino and alkylmercapto with in each case 1 or 2 carbon atoms in the alkyl groups; R^1 and $R^{1'}$ are identical or different and each represent a straight-chain or branched hydrocarbon radical which has up to 6 carbon atoms and is optionally interrupted in the chain by an oxygen and is optionally substituted by fluorine, chlorine, hydroxyl, phenyl or phenoxy; R^2, $R^{2'}$, R^4 and $R^{4'}$ are identical or different and each represent a hydrogen atom or a straight-chain, or branched alkyl radical which has up to 4 carbon atoms and is optionally substituted by fluorine, chlorine, hydroxyl, phenyl or amino; R^3 and $R^{3'}$ are identical or different and each represents a hydrogen atom, an alkyl radical with 1 to 4 carbon atoms or a phenyl, benzyl or phenethyl radical which is optionally substituted by hydroxyl, fluorine or chlorine,

B

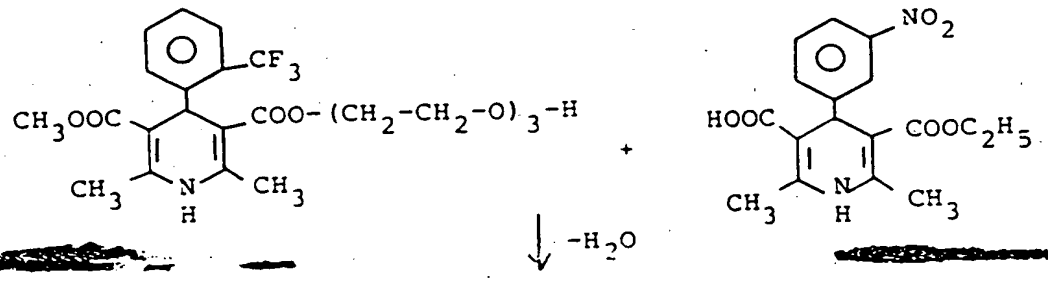
Y and Y' are in each case identical or different and denote -COO-, -CONH-, -CO- or $-SO_2-$, and X represents a bridge member which has at least one CH_2 group which is not bonded to the rings and at most 9 adjacent CH_2 groups as chain members, it being possible for the bridge member additionally to contain, in any desired sequence, 1 to 3 identical or different chain members selected from O, S, CO, CS, NR^5, $C(R^6)_2$, CH=N, phenylene, naphthylene, pyridylene, cycloalkylene with 5 to 7 carbon atoms, piperazinylene, piperidinylene, pyrrolidinylene and morpholinylene,

wherein

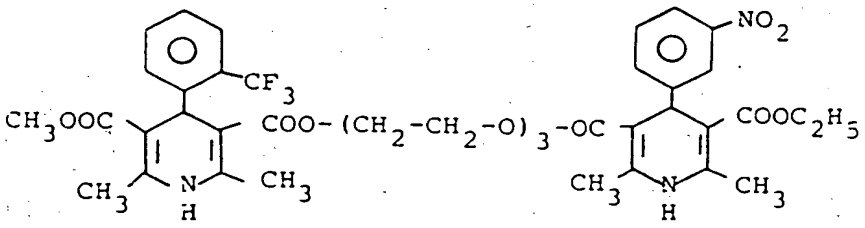
R^5 represents a hydrogen atom a benzyl radical or an alkyl radical with 1 to 4 carbon atoms, and R^6 represents a hydrogen atom, a benzyl or phenyl radical, a fluorine or chlorine atom, an alkyl radical with 1 to 4 carbon atoms or a hydroxyl, trifluoromethyl, cyano, carboxyl or amino radical.

Using the particular starting substances shown, the synthesis of the compounds of the general formula (I) according to the invention by the individual process variants is illustrated by the following equations:

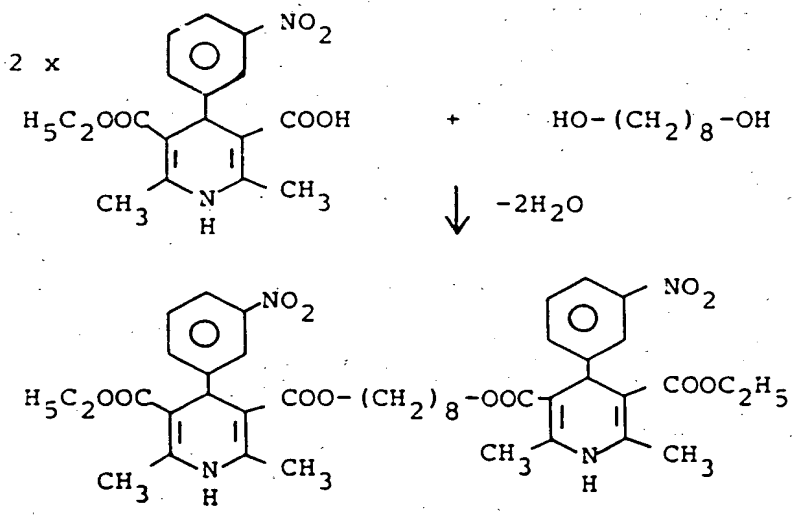
Process variant (a)



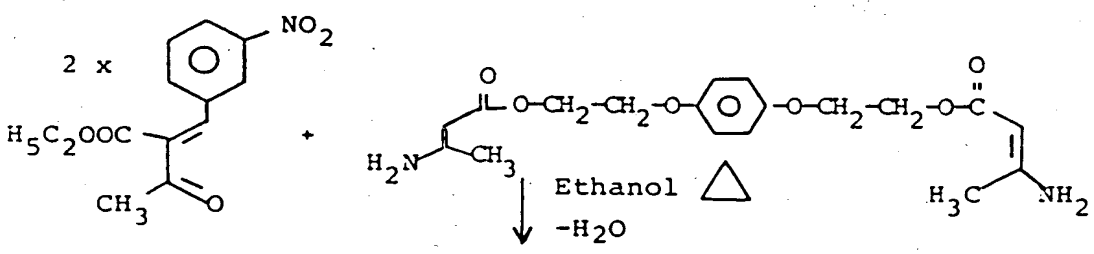
B.

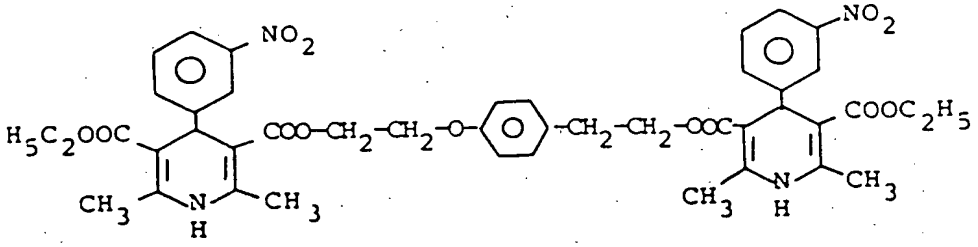


Process variant (b)



Process variant (c)





The hydroxy-1,4-dihydropyridine derivatives of the formula (II) used as starting substances and the dihydropyridine-3-carboxylic acid derivatives of the formula (III) are known, or they can be prepared by known methods (see DT-OS (German Published Specification) 2,117,571).

The 1,4-dihydropyridinecarboxylic acids of the general formula (IV) are known, or they can be prepared by known methods (compare European Published Specification) 11,706).

The bifunctional compounds of the general formula (V) are likewise known, or they can be prepared by known methods (see Beilstein, Volume I, 464 to 502).

The ylidene-β-keto esters of the general formula (VI) are known, or they can be prepared by processes which are known from the literature (see G. Jones, The "Knoevenagel-Condensation", in Organic Reactions, Volume XV, 204 et seq. (1967)).

The enaminocarboxylic acid esters of the general formula (VII) used as starting substances are known, or they can likewise be prepared by methods which are known from the literature (see [illegible] Am. [illegible] 67, 1017 (1945)).

Possible diluents for use in process variants (a) and (b) are any of the aprotic organic solvents. These include, preferably, ethers (such as dioxane, diethyl ether,

tetrahydrofuran and glycol dimethyl ether), hydrocarbons (such as benzene, toluene or xylene) and dimethylformamide, dimethylsulphoxide, acetonitrile, pyridine or hexamethylphosphoric acid triamide.

In the case of process variant (c), alcohols (for example methanol, ethanol or isopropanol) can also advantageously be employed as diluents.

Water-binding agents (for process variants (a) and (b)) which can be used are any of the reagents customary for this, and the use of dicyclohexylcarbodiimide and the addition of a catalyst, such as 4-dimethylaminopyridine, are particularly advantageous.

The reaction temperature can be varied within the substantial range of between 0 and 180°C, preferably between 20 and 120°C.

The reactions can be carried out under normal pressure or under increased pressure. In general, they are carried out under normal pressure.

The compounds of the present invention exhibit interesting biological actions. They have a broad and diverse pharmacological action spectrum and are distinguished, in particular, by their long-lasting action. The following main actions may be mentioned specifically:

1. On parenteral, oral and perlingual administration, the compounds produce a distinct and long-lasting dilation of the coronary vessels. This action on the coronary vessels is intensified by a simultaneous nitrite-like effect of reducing the load on the heart.

They influence or modify the heart metabolism in the sense of an energy saving.

2. The excitability of the stimulus formation and excitation conduction system within the heart is lowered, [illegible] demonstrable at therapeutic doses results.

3. The tone of the smooth muscle of the vessels is

greatly reduced under the action of the compounds. This vascular-spasmolytic action can take place in the entire vascular system or can manifest itself as more or less isolated in circumscribed vascular regions (such as, for example, the central nervous system).

4. The compounds lower the blood pressure of normotonic and hypertonic animals and can thus be used as antihypertensive agents.

5. The compounds have strongly muscular-spasmolytic actions which manifest themselves on the smooth muscle of the stomach, the intestinal tract, the urogenital tract and the respiratory system.

As stated above, the invention also relates to the use in human and veterinary medicine of the compounds of the invention.

The present invention provides a pharmaceutical composition containing as active ingredient a compound of the invention in admixture with a solid or liquefied gaseous diluent, or in admixture with a liquid diluent other than a solvent of a molecular weight less than 200 (preferably less than 350) except in the presence of a surface active agent.

The invention further provides a pharmaceutical composition containing as active ingredient a compound of the invention in the form of a sterile and/or physiologically isotonic aqueous solution.

The invention also provides a medicament in dosage unit form comprising a compound of the invention.

The invention also provides a medicament in the form of tablets (including lozenges and granules), dragees, capsules, pills, ampoules or suppositories comprising a compound of the invention.

"Medicament" as used in this Specification means physically discrete coherent portions suitable for medical administration. "Medicament in dosage unit form" as

used in this Specification means physically discrete coherent units suitable for medical administration each containing a daily dose or a multiple (up to four times) or submultiple (down to a fortieth) of a daily dose of the compound of the invention in association with a carrier and/or enclosed within an envelope. Whether the medicament contains a daily dose or, for example, a half, a third or a quarter of a daily dose will depend on whether the medicament is to be administered once or, for example, twice, three times or four times a day respectively.

The pharmaceutical composition according to the invention may, for example, take the form of sprays (including aerosols), suspensions, solutions and emulsions of the active ingredient in aqueous or non-aqueous diluents, syrups, granulates or powders.

The diluents to be used in pharmaceutical compositions (e.g. granulates) adapted to be formed into tablets, dragees, capsules and pills include the following: (a) fillers and extenders, e.g. starch, sugars, mannitol, and silicic acid; (b) binding agents, e.g. carboxymethyl cellulose and other cellulose derivatives, alginates, gelatine and polyvinyl pyrrolidone; (c) moisturizing agents, e.g. glycerol; (d) disintegrating agents, e.g. agar-agar, calcium carbonate and sodium bicarbonate; (e) agents for retarding dissolution e.g. paraffin; (f) resorption accelerators, e.g. quaternary ammonium compounds; (g) surface active agents, e.g. cetyl alcohol, glycerol monostearate; (h) adsorptive carriers, e.g. kaolin and bentonite; (i) lubricants, e.g. talc, calcium and magnesium stearate and solid polyethyl glycols.

The tablets, dragees, capsules and pills formed from the pharmaceutical compositions of the invention can have the customary coatings, envelopes and protective matrices, which may contain opacifiers. They can be

so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes and protective matrices may be made, for example, of polymeric substances or waxes.

The ingredient can also be made up in micro-encapsulated form together with one or several of the above-mentioned diluents.

The diluents to be used in pharmaceutical compositions adapted to be formed into suppositories can, for example, be the usual water-soluble diluents, such as polyethylene glycols and fats (e.g. cocoa oil and high esters (e.g. C_{14}-alcohol with C_{16}-fatty acid)) or mixtures of these diluents.

The pharmaceutical compositions which are powders and sprays can, for example, contain the usual diluents, e.g. lactose, talc, silicic acid, aluminium hydroxide, calcium silicate, and polyamide powder or mixtures of these substances. Aerosol sprays can, for example, contain the usual propellants, e.g. chlorofluorohydrocarbons.

The pharmaceutical compositions which are solutions and emulsions can, for example, contain the customary diluents (with, of course, the above-mentioned exclusion of solvents having a molecular weight below 200 except in the presence of a surface-active agent), such as solvents, dissolving agents and emulsifiers; specific examples of such diluents are water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene

glycol, dimethylformamide, oils (for example ground nut oil), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitol or mixtures thereof.

For parenteral administration, solutions and emulsions should be sterile, and, if appropriate, blood-isotonic.

The pharmaceutical compositions which are suspensions can contain the usual diluents, such as liquid diluents, e.g. water, ethyl alcohol, propylene glycol, surface-active agents (e.g. ethoxylated isostearyl alcohols, polyoxyethylene sorbite and sorbitane esters), microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth or mixtures thereof.

All the pharmaceutical compositions according to the invention can also contain colouring agents and preservatives as well as perfumes and flavouring additions (e.g. peppermint oil and eucalyptus oil) and sweetening agents (e.g. saccharin).

The pharmaceutical compositions according to the invention generally contain from 0.5 to 90% of the active ingredient by weight of the total composition.

In addition to a compound of the invention, the pharmaceutical compositions and medicaments according to the invention can also contain other pharmaceutically active compounds. They may also contain a plurality of compounds of the invention.

Any diluent in the medicaments of the present invention may be any of those mentioned above in relation to the pharmaceutical compositions of the present invention. Such medicaments may include solvents of molecular weight less than 200 as sole diluent.

The discrete coherent portions constituting the medicament according to the invention will generally be adapted by virtue of their shape or packaging for

medical administration and may be, for example, any of the following: tablets (including lozenges and granulates), pills, dragees, capsules, suppositories and ampoules. Some of these forms may be made up for delayed release of the active ingredient. Some, such as capsules, include a protective envelope which renders the portions of the medicament physically discrete and coherent.

The preferred daily dose for intravenous administration of the medicaments of the invention is 2.5 mg to 250 mg of active ingredient, and for oral administration of medicaments of the invention is 25 to 250 mg of active ingredient.

The production of the above-mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredient(s) with the diluent(s) to form a pharmaceutical composition (e.g. a granulate) and then forming the composition into the medicament (e.g. tablets).

This invention further provides a method of combating (including prevention, relief and cure of) the above-mentioned diseases in human and non-human animals, which comprises administering to the animals a compound of the invention alone or in admixture with a diluent or in the form of a medicament according to the invention.

It is envisaged that these active compounds will be administered perorally, parenterally (for example intramuscularly, intraperitoneally, subcutaneously and intravenously), or rectally, preferably orally or parenterally, in particular perlingually or intravenously. Preferred pharmaceutical compositions and medicaments are therefore those adapted for administration such as oral or parenteral administration. Administration

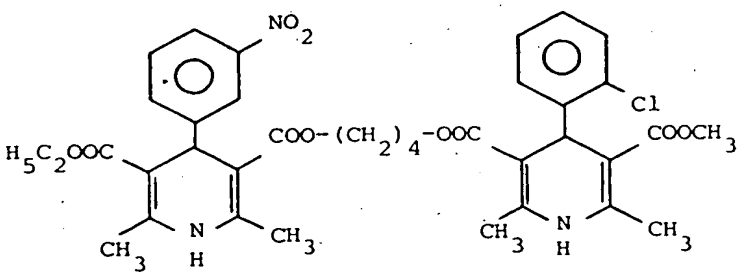
in the method of the invention is preferably oral or parenteral administration.

In general it has proved advantageous to administer intravenously amounts of from 0.01 mg to 10 mg/kg, preferably 0.05 mg to 5 mg/kg, of body weight per day or to administer orally from 0.05 mg to 20 mg/kg, preferably 0.5 mg to 5 mg/kg, of body weight per day, to achieve effective results. Nevertheless, it can at times be necessary to deviate from those dosage rates, and in particular to do so as a function of the nature and body weight of the human or animal subject to be treated, the individual reaction of this subject to the treatment, the type of formulation in which the active ingredient is administered and the mode in which the administration is carried out, and the point in the progress of the disease or interval at which it is to be administered. Thus it may in some case suffice to use less than the above-mentioned minimum dosage rate, whilst other cases the upper limit mentioned must be exceeded to achieve the desired results. Where larger amounts are administered it can be advisable to divide these into several individual administrations over the course of the day.

Processes for the production of compounds according to the present invention are illustrated by the following Examples.

Example 1

Butanediyl 1-[2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate] 4-[2,6-dimethyl-5-methoxycarbonyl-4-(2-chlorophenyl)-1,4-dihydropyridine-3-carboxylate]



(Process variant (a))

25 mmoles of 2,6-dimethyl-5-(4-hydroxybutoxy)-carbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid ethyl ester were dissolved in 50 ml of anhydrous dimethylformamide together with 25 mmoles of dicyclohexylcarbodiimide and 25 mmoles of 2,6-dimethyl-5-methoxycarbonyl-4-(2-chlorophenyl)-1,4-dihydropyridine-3-carboxylic acid and the solution was heated to 100°C for 4 hours, with the addition of 0.2 g of 4-dimethylaminopyridine. The mixture was then filtered and the filtrate was diluted with methylene chloride, extracted by shaking with aqueous NaOH and with HCl, dried, and concentrated in a rotary evaporator.

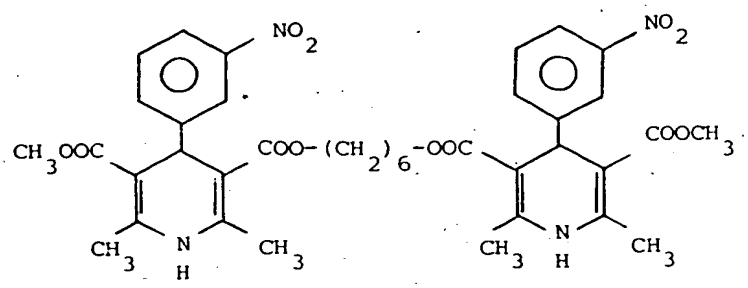
The residue was then chromatographed on silica gel using ether.

Yield: 25%, amorphous foam.

^{1}H-NMR: δ = 1.2 (t,3H), 1.4-1.8 (m, 4H), 2.4 (s,12H), 3.6 (s,3H), 3.9-4.4 (m,6H), 5.2 (s,1H), 5.4 (s,1H), 5.8 (s,NH), 6.3 (s,NH) and 6.9-8.3 (m,8H).

Example 2

Hexanediyl 1,6-bis-[2,6-dimethyl-5-methoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]



(Process variant (b))

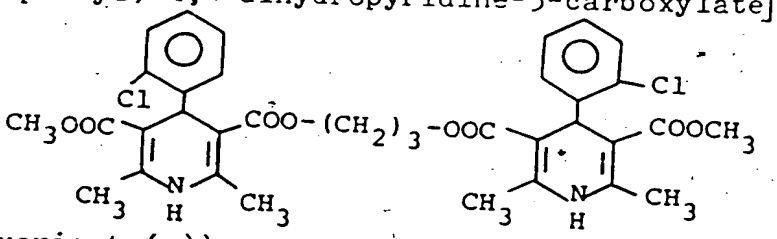
B

50 mmoles of 2,6-dimethyl-5-methoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid were dissolved in 50 ml of anhydrous dimethylformamide together with 50 mmoles of dicyclohexylcarbodiimide and 25 mmoles of hexane-1,6-diol and the solution was stirred at 100°C for 4 hours, with the addition of 0.2 g of 4-dimethylaminopyridine. The mixture was then filtered, the filtrate was diluted with methylene chloride, extracted by shaking with aqueous NaOH and with HCl, dried, and concentrated in a rotary evaporator, and the residue was recrystallised from methanol.

Melting point: 177-179°C, yield: 37%.

Example 3

Propanediyl 1,3-bis-[2,6-dimethyl-5-methoxycarbonyl-4-(2-chlorophenyl)-1,4-dihydropyridine-3-carboxylate]



(Process variant (c))

25 mmoles of propanediyl 1,3-bis-(3-aminocrotonate) and 50 mmoles of 2-chlorobenzylideneacetoacetic acid methyl ester in 100 ml of absolute ethanol were boiled under reflux and under N_2 for 14 hours.

After the mixture had cooled, the solvent was distilled off in vacuo and the residue was taken up in 50% strength aqueous ethanol. The semi-solid residue was recrystallised from methanol.

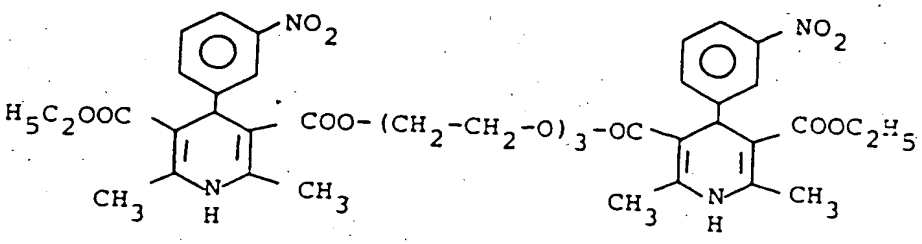
Melting point: 200 to 203°C; yield: 50%.

Example 4

A

Triethylene glycol bis-[2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]

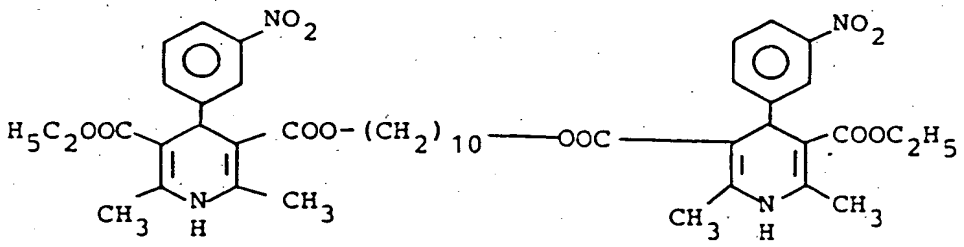
B1



Analogously to Example 2, 100 mmoles of 2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid were reacted with 50 mmoles of triethylene glycol and the mixture was worked up.
Melting point: 113 to 120°C; yield: 32%.

Example 5

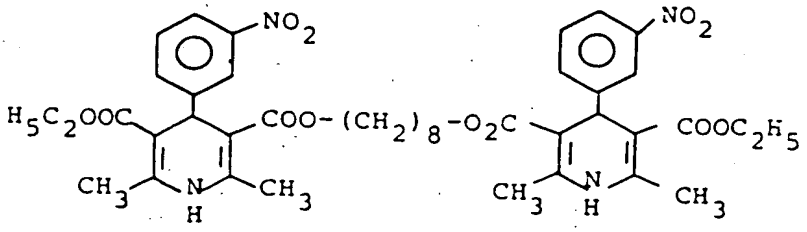
Decanediyl 1,10-bis-[2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]



100 mmoles of 2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid were reacted with 50 mmoles of 1,10-decanediol analogously to Example 2.
Melting point: 121 to 125°C; yield: 35%.

Example 6

Octanediyl 1,8-bis-[2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl-1,4-dihydropyridine-3-carboxylate]

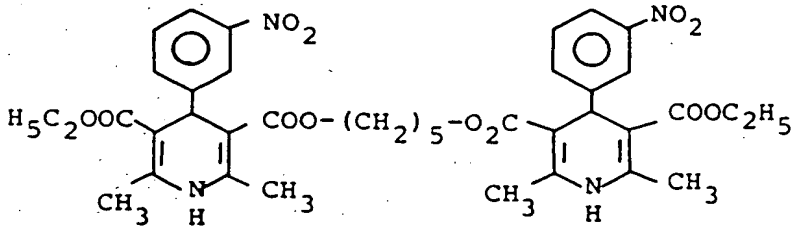


Analogously to Example 2, 100 mmoles of 2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid were reacted with 50 mmoles of 1,8-octanediol.

Melting point: 170 to 184°C; yield: 47%.

Example 7

Pentanediyl 1,5-bis-[2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl-1,4-dihydropyridine-3-carboxylate]



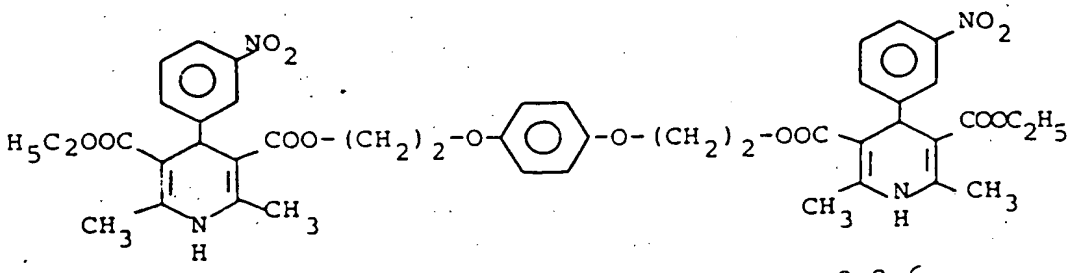
Analogously to Example 2, 100 mmoles of 2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid were reacted with 50 mmoles of 1,5-pentanediol.

Melting point: 145°C; yield: 11%.

Example 8

1,4-bis-(2-hydroxyethoxy)-benzene bis-[2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]

B.

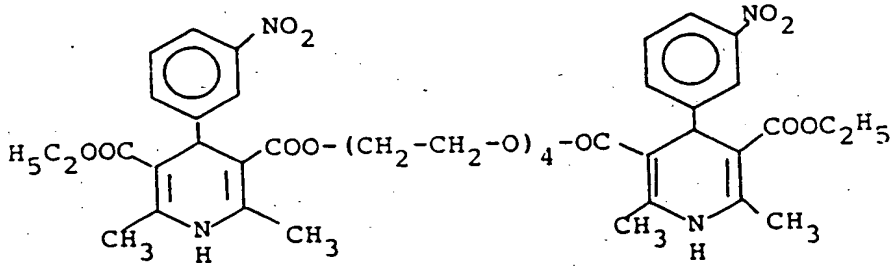


Analogously to Example 2, 100 mmoles of 2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid were reacted with 50 mmoles of 1,4-bis-(2-hydroxyethoxy)-benzene.

Melting point: 160 to 190°C (decomposition); yield: 49%.

Example 9

Tetraethylene glycol bis-[2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]



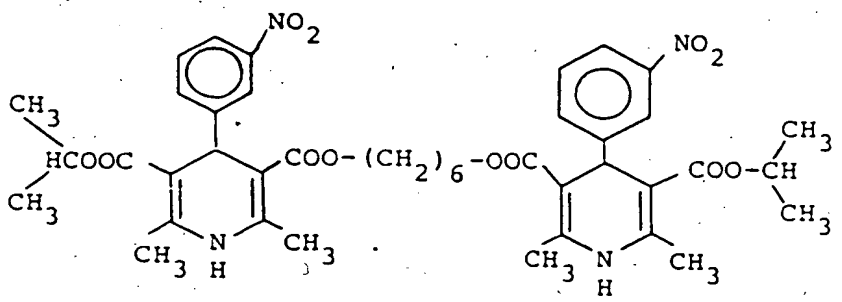
Analogously to Example 2, 100 mmoles of 2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid were reacted with 50 mmoles of tetraethylene glycol and the mixture was worked up.

Melting point: 93 to 98°C yield: 16%.

Example 10

Hexanediyl 1,6-bis-[2,6-dimethyl-5-isopropoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]

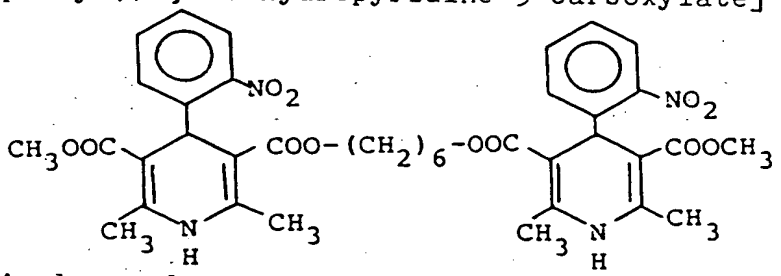
B)



Analogously to Example 3, 25 mmoles of hexanediyl 1,6-bis-(3-aminocrotonate) were reacted with 50 mmoles of 3-nitrobenzylideneacetoacetic acid diisopropyl ester.
Melting point: 120 to 136°C yield: 83%.

Example 11

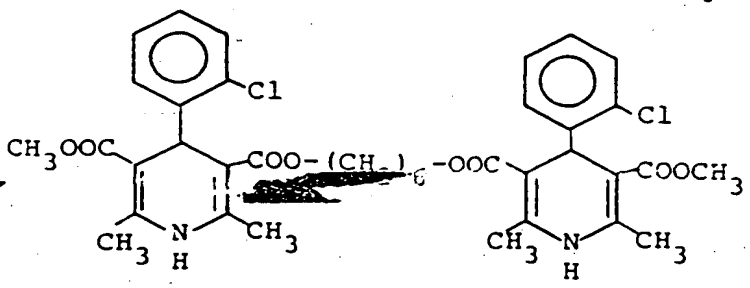
Hexanediyl 1,6-bis-[2,6-dimethyl-5-methoxycarbonyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]



Analogously to Example 3, 25 mmoles of hexanediyl 1,6-bis-(3-aminocrotonate) were reacted with 50 mmoles of 2-nitrobenzylideneacetoacetic acid methyl ester.
Melting point: 88 to 95°C yield: 82%.

Example 12

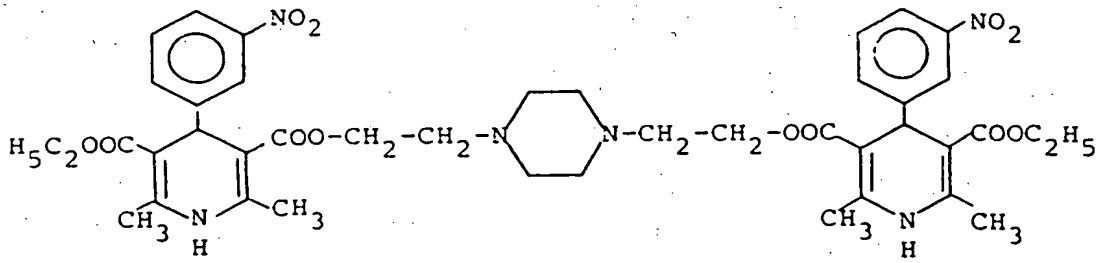
Hexanediyl bis-[2,6-dimethyl-5-methoxycarbonyl-4-(2-chlorophenyl)-1,4-dihydropyridine-3-carboxylate]



Analogously to Example 3, 25 mmoles of hexanediyl 1,6-bis-(3-aminocrotonate) were reacted with 50 mmoles of 2-chlorobenzylideneacetoacetic acid methyl ester.
Melting point: 152 to 158°C. yield: 27%.

Example 13

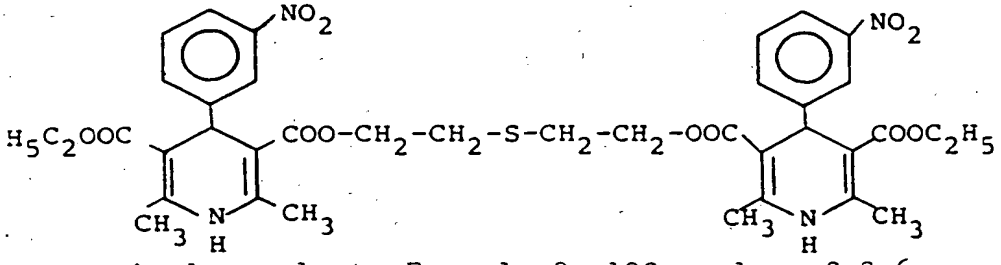
N,N'-bis-(2-hydroxyethyl)-piperaxine bis-[2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]



Analogously to Example 2, 100 mmoles of 2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid were reacted with 50 mmoles of N,N'-bis-(2-hydroxyethyl)-piperazine.
Melting point: 203 to 208°C yield: 18%.

Example 14

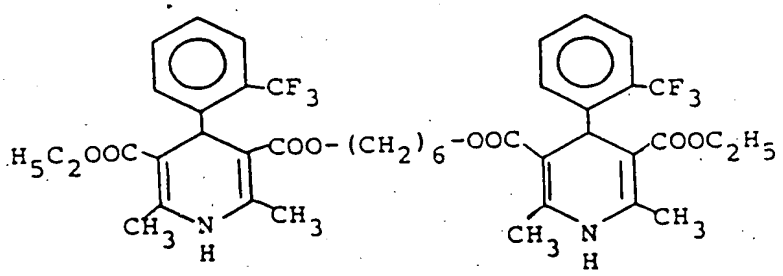
Bis-hydroxyethyl sulphide bis-[2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]



Analogously to Example 2, 100 mmoles of 2,6-dimethyl-5-ethoxycarbonyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid were reacted with 50 [illegible] of bis-hydroxyethyl sulphide.
Yield: 70%.

Example 15

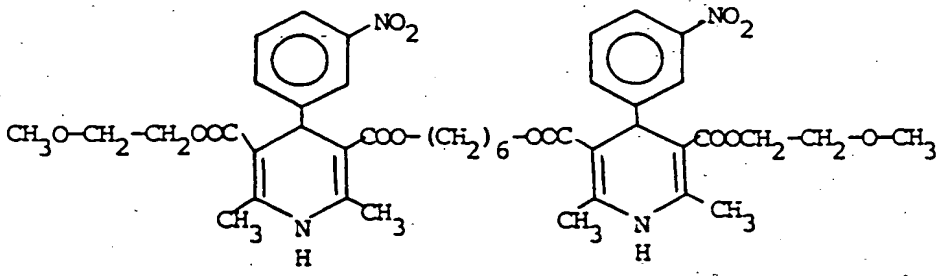
Hexanediyl 1,6-bis-[2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]



Analogously to Example 3, 25 mmoles of hexanediyl 1,6-bis-(3-aminocrotonate) were reacted with 50 mmoles of 2-trifluoromethylbenzylideneacetoacetic acid ethyl ester. Melting point: 129 to 139°C yield 49%.

Example 16

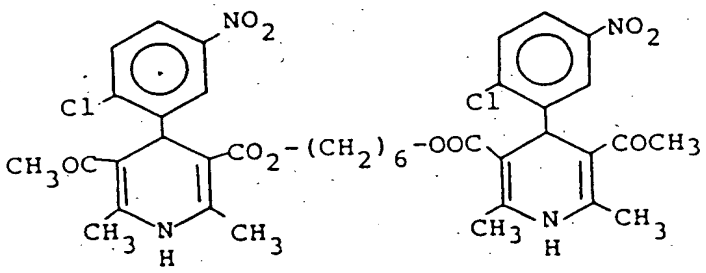
Hexanediyl 1,6-bis-[2,6-dimethyl-5-(2-methoxy)-ethoxy-carbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]



Analogously to Example 3, 25 mmoles of hexanediyl 1,6-bis-(3-aminocrotonate) were reacted with 50 mmoles of 3-nitrobenzylideneacetoacetic acid 2-methoxy ethyl ester. Melting point: 144 to 156°C yield: 50%.

Example 17

Hexanediyl 1,6-bis-[2,6-dimethyl-5-methylcarbonyl-4-(2-chloro-5-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]

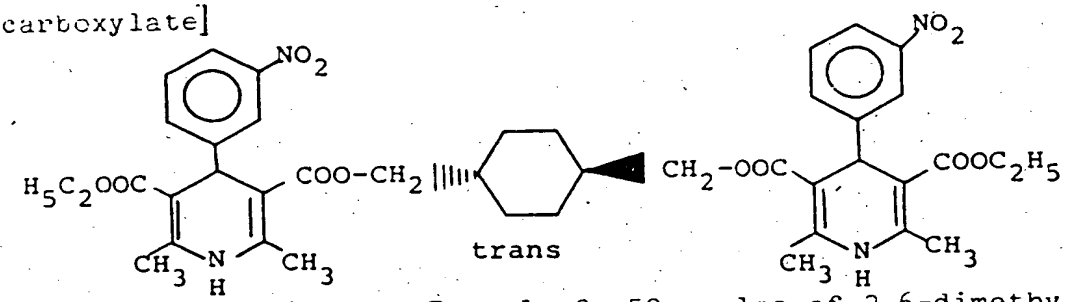


Analogously to Example 3, 25 mmoles of hexanediyl 1,6-bis-(3-aminocrotonate) were reacted with 50 mmoles of 2-chloro-5-nitro-benzylidene-2,4-butanedione.

Melting point: 147 to 153°C yield: 46%.

Example 18

E-1,4-Bis(hydroxymethyl)cyclohexane bis-[2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]

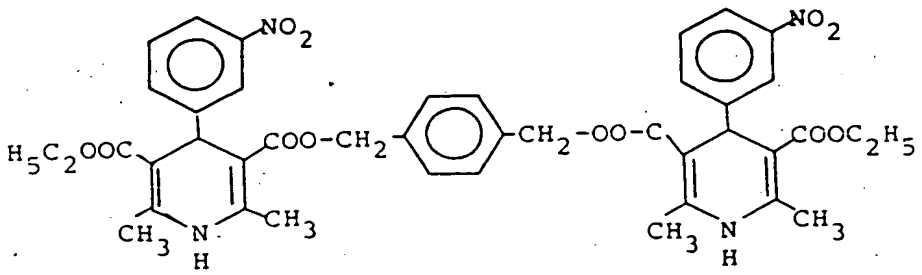


Analogously to Example 2, 50 mmoles of 2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid were reacted with 25 mmoles of E-1,4-bis-(hydroxymethyl)-cyclohexane.

Melting point: 172 to 188°C yield: 15%.

Example 19

1,4-Bis-(hydroxymethyl)-benzene bis-[2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]

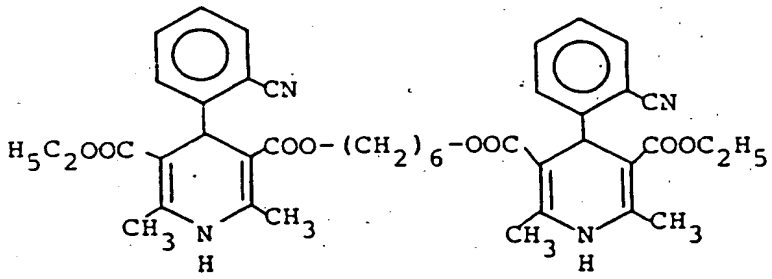


Analogously to Example 2, 50 mmoles of 2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid were reacted with 25 mmoles of 1,4-bis-(hydroxymethyl)-benzene.

Melting point: 244 to 59°C yield: 30%.

Example 20

Hexanediyl 1,6-bis-[2,6-dimethyl-5-ethoxycarbonyl-4-(2-cyanophenyl)-1,4-dihydropyridine-3-carboxylate]

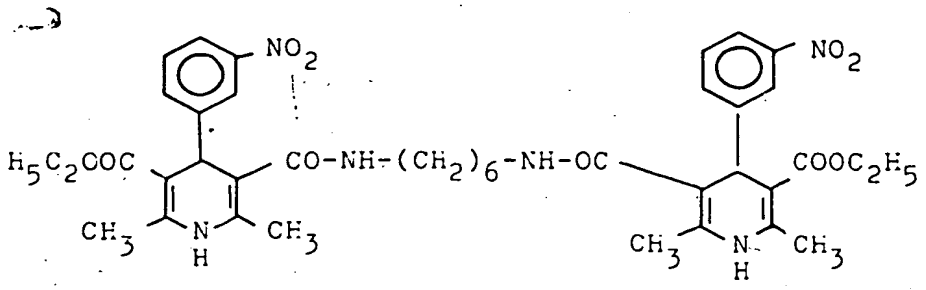


Analogously to Example 3, 25 mmoles of hexanediyl 1,6-bis-[3-aminocrotonate) were reacted with 50 mmoles of 2-cyanobenzylideneacetoacetic acid ethyl ester.

Yield: 80%.

Example 21

Bis-[2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid] 1,6-hexanediylamide

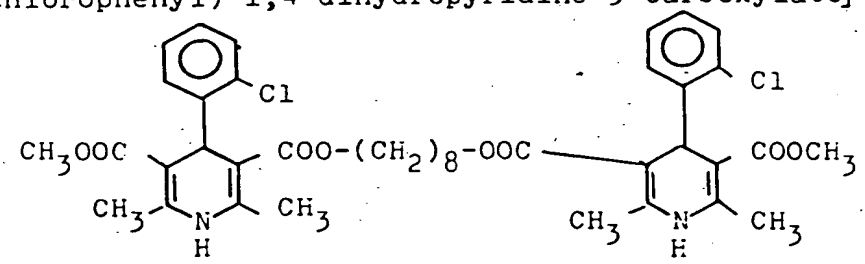


Analogously to Example 2, 25 mmoles of 2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid were reacted with 12.5 mmoles of 1,6-diaminohexane.

Yield: 27% (melting point: 147 to 152°C).

Example 22

Octanediyl 1,8-bis-[2,6-dimethyl-5-methoxycarbonyl-4-(2-chlorophenyl)-1,4-dihydropyridine-3-carboxylate]



Analogously to Example 3, 25 mmoles of hexanediyl 1,6-bis-(3-aminocrotonate) were reacted with 50 mmoles of 2-chlorobenzylideneacetoacetic acid methyl ester.

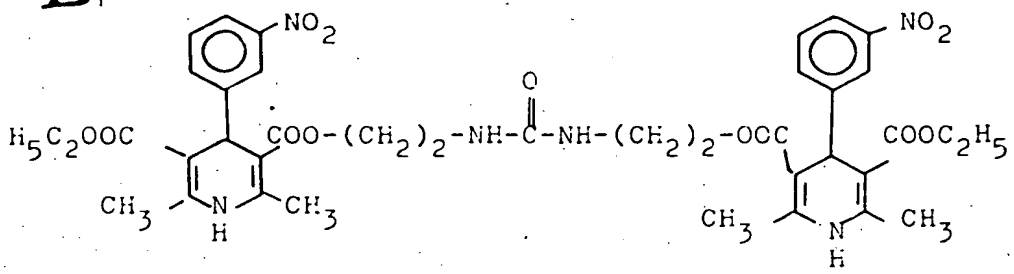
Yield: 80% of amorphous substance.

^{1}H-NMR ($CDCl_3$): δ = 1.0-1.4 (m, 8H), 1.4-1.7 (m, 4H), 2.2 (2s, 12H), 3.6 (s, 6H), 4.0 (t, 4H), 5.4 (s, 2H), 5.9 (s, NH) and 6.9-7.5 (m, 8H).

Example 23

N,N'-Bis-hydroxyethylurea bis-[2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]

B.

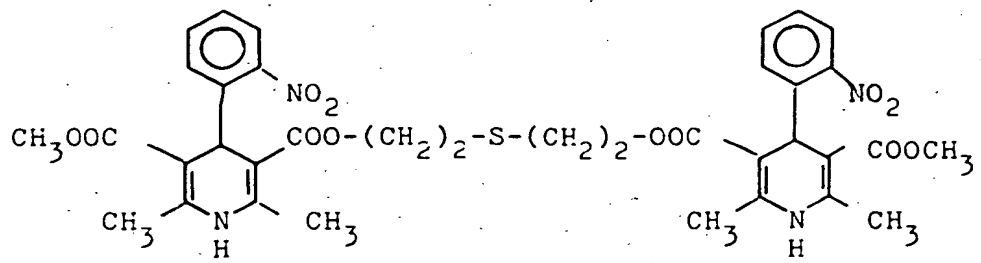


This compound was prepared analogously to Example 2 from N,N'-bishydroxyethylurea and 2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid.

Yield: 32%, melting point: 178 to 187°C.

Example 24

Bis-(2-hydroxyethyl)-sulphide bis-[2,6-dimethyl-5-methoxycarbonyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]



This compound was prepared analogously to Example 3 from bis-(2-hydroxyethyl) sulphide bis-(3-aminocrotonate) and 2-nitrobenzylideneacetoacetic acid methyl ester.

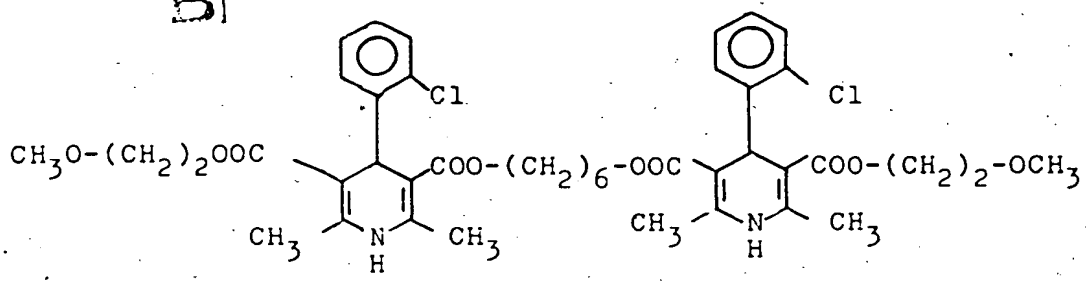
Yield: 80% of amorphous substance

^{1}H-NMR ($CDCl_3$): δ = 2.3 (2s, 12H), 2.4-2.8 (m, 4H), 3.6 (s, 6H), 3.9-4.3 (m, 4H), 5.8 (s, 2H), 6.3 (s, NH) and 7.1-7.8 (m, 8H).

Example 25

Hexanediyl 1,6-bis-[2,6-dimethyl-5-(2-methoxy)-ethoxycarbonyl-4-(2-chlorophenyl)-1,4-dihydropyridine-3-carboxylate]

B1

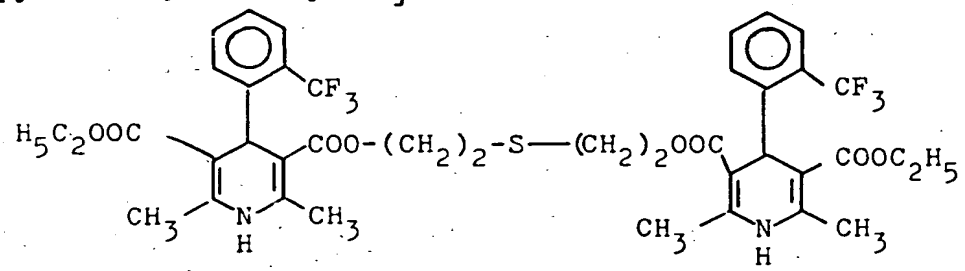


This compound was prepared analogously to Example 3 from 25 mmoles of hexanediyl 1,6-bis-(3-aminocrotonate) and 50 mmoles of 2-chlorobenzylideneacetoacetic acid 2-methoxyethyl ester.

Yield: 67% (melting point: 135 to 143°C).

Example 26

Bis-(2-hydroxyethyl)-sulphide bis-[2,6-dimethyl-5-ethoxycarbonyl-4-(2-trifluoromethylphenyl)-1,4-dihydropyridine-3-carboxylate]



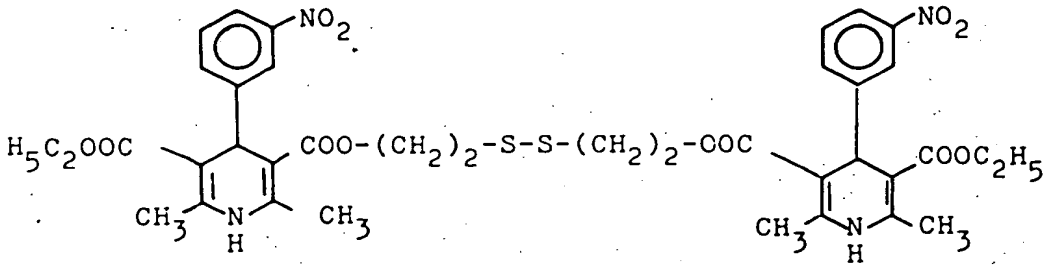
This compound was prepared analogously to Example 3 from 25 mmoles of bis-(2-hydroxyethyl)-sulphide bis-(3-aminocrotonate) and 2-trifluoromethylbenzylidene-acetoacetic acid ethyl ester.

Yield: 79% of amorphous substance.

^{1}H-NMR ($CDCl_3$): δ = 1.2 (t, 6H), 2.2 (s, 12H), 2.4-2.8 (m, 4H), 3.9-4.5 (m, 8H), 5.6 (s, 2H), 6.7 (s, NH) and 7.1-7.7 (m, 8H).

Example 27

Bis-([illegible]-bis-[2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]



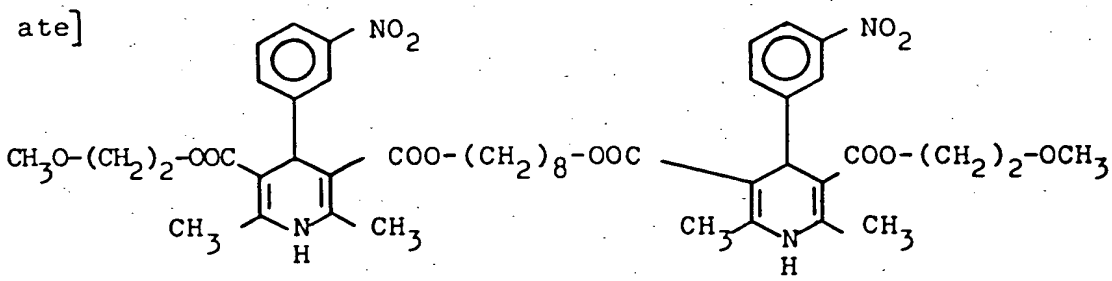
Analogously to Example 2, 12.5 mmoles of bis-(2-hydroxyethyl)-disulphide were reacted with 25 mmoles of 2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid.

Yield: 77% of amorphous substance.

^{1}H-NMR ($CDCl_3$): δ = 1.2 (t, 6H), 2.4 (s, 12H), 2.7-3.1 (m, 4H), 3.9-4.5 (m, 8H), 5.1 (s, 2H), 6.4 (s, NH) and 7.2-8.2 (m, 8H).

Example 28

Octanediyl 1,8-bis-[2,6-dimethyl-5-(2-methoxyethoxycarbonyl)-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]



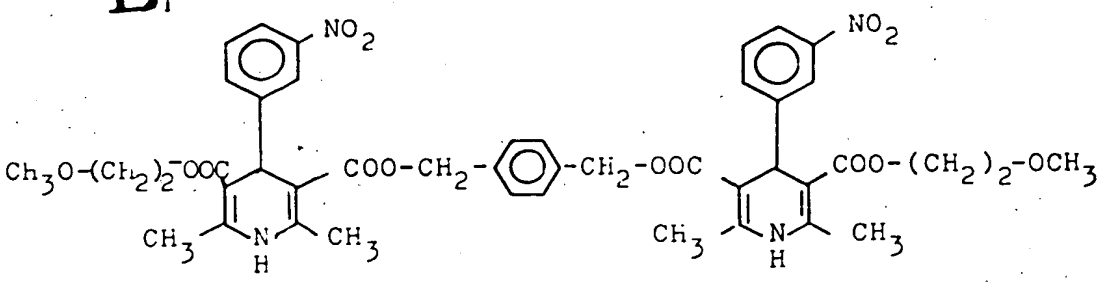
Analogously to Example 3, 25 mmoles of octanediyl 1,8-bis-(3-aminocrotonate) were reacted together with 50 mmoles of 3-nitrobenzylideneacetoacetic acid 2-methoxy ethyl ester.

Yield: 75% (melting point: 146 to 150°C).

Example 29

1,4-Bis-(hydroxymethyl)-benzene bis-[2,6-dimethyl-5-(2-methoxyethoxycarbonyl)-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate]

Bi

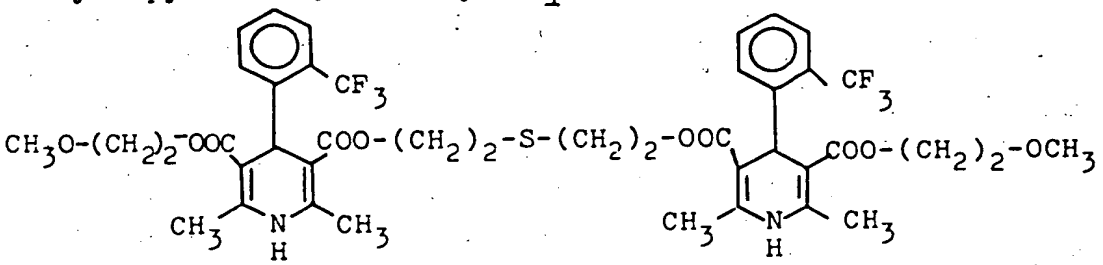


This compound was prepared analogously to Example 3 from 25 mmoles of 1,4-bis-(hydroxymethyl)-benzene bis-(3-aminocrotonate) and 50 mmoles of 3-nitrobenzylidene-acetoacetic acid 2-methoxyethyl ester.

Yield: 67% (melting point: 159 to 162°C).

Example 30

Bis-(2-hydroxyethyl)-sulphide bis-[2,6-dimethyl-5-(2-methoxyethoxycarbonyl)-4-(2-trifluoromethylphenyl)-1,4-dihydropyridine-3-carboxylate]

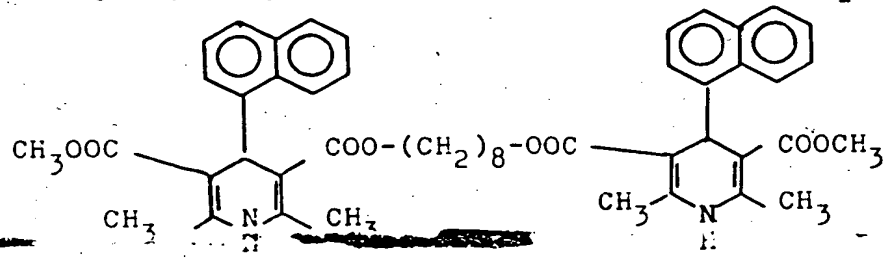


This compound was prepared analogously to Example 3.

Yield: 28% (melting point: 100 to 112°C).

Example 31

Octanediyl 1,8-bis-[2,6-dimethyl-5-methoxycarbonyl-4-(1-naphthyl)-1,4-dihydropyridine-3-carboxylate]



This compound was prepared analogously to Example 3.

Yield: 76% of amorphous substance.

^{1}H-NMR ($CDCl_3$): δ = 0.8-1.5 (m, 12H), 2.3 (2s, 12H), 3.5 (s, 6H), 3.6-4.1 (m, 4H), 5.8 (s, 2H), 6.1 (s, NH) and 7.1-7.8 (m, 14H).

Among the new 1,4-dihydropyridine compound salts of the invention, those salts that are pharmaceutically acceptable are particularly important and are preferred.

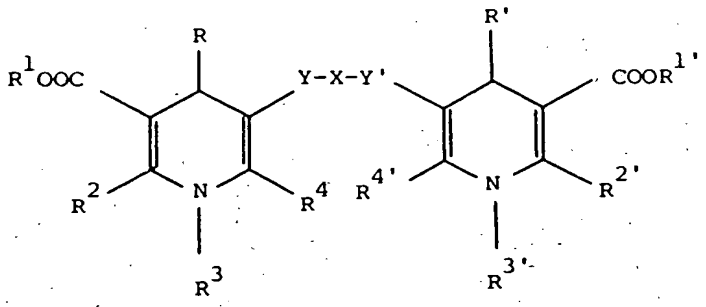
The new free 1,4-dihydropyridine compounds of the general formula (I) and their salts can be interconverted in any suitable manner; methods for such interconversion are known in the art.

The present invention also comprises pharmaceutically acceptable bioprecursors of the active compounds of the present invention.

For the purposes of this specification the term 'pharmaceutically acceptable bioprecursor' of an active compound of the invention means a compound having a structural formula different from the active compound but which nonetheless, upon administration to an animal or human being is converted in the patient's body to the active compound.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A process for preparing 1,4-dihydropyridines which are linked in the C-3 position, of the general formula



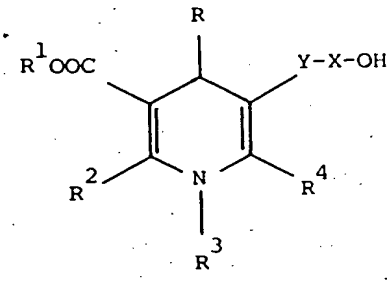
I

and pharmaceutically acceptable salts thereof, in which R and R' are identical or different and each represents a phenyl or naphthyl radical or a heterocyclic radical selected from thienyl, furyl, pyrryl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, quinolyl, isoquinolyl, indolyl, benzimidazolyl, quinazolyl, or quinoxalyl radical, the aryl or heterocyclic radical optionally carrying 1 or 2 identical or different substituents selected from phenyl, alkyl with 1 to 8 carbon atoms, cycloalkyl with 3 to 7 carbon atoms, alkenyl or alkinyl with in each case 2 to 6 carbon atoms, alkoxy, alkenoxy or alkinoxy with in each case up to 4 carbon atoms, an alkylene chain with 3 to 6 carbon atoms, dioxyalkylene with 1 or 2 carbon atoms, halogen, trifluoromethyl, trifluoromethoxy, difluoromethoxy, tetrafluoroethoxy, nitro, cyano, azido, hydroxyl, amino, mono- or di-alkylamino with in each case 1 to 4 carbon atoms per alkyl group, carboxyl, carbalkoxy with 2 to 4 carbon atoms, carboxamido, sulphonamido and sulphonylalkyl or alkylmercapto with in each case 1 to 4 carbon atoms per alkyl radical; R^- and R^- are identical or different and each represent a straight-chain, branched or cyclic, saturated hydrocarbon radical which has up to 8 carbon atoms and is optionally interrupted in the chain by 1 or 2 oxygen atoms and is optionally substituted

by fluorine, chlorine, hydroxyl, phenyl, phenoxy, phenylthio or phenylsulphonyl, the phenyl radicals in turn optionally being substituted by 1 or 2 identical or different substituents selected from nitro, trifluoromethyl, cyano, fluorine, chlorine and alkyl and dialkylamino with in each case 1 to 4 carbon atoms in the alkyl radicals; R^2, $R^{2'}$, R^4 and $R^{4'}$ are identical or different and each represent a hydrogen atom or a straight-chain, branched or cyclic, saturated or unsaturated hydrocarbon radical which has up to 8 carbon atoms and is in turn optionally substituted by fluorine, chlorine, hydroxyl, phenyl, amino, alkylamino or cycloalkyl with up to 6 carbon atoms; R^3 and $R^{3'}$ are identical or different and each represent a hydrogen atom or a straight-chain or branched alkyl radical which has up to 8 carbon atoms and optionally is interrupted in the chain by an oxygen atom or is substituted by hydroxyl or halogen, or represent optionally substituted phenyl, benzyl or phenethyl radical; Y and Y' are in each case identical or different and each denote -COO-, -CONH-, -CO-, -COS- or $-SO_2-$ and X represents a bridge member which has at least one CH_2 group which is not bonded to the rings and at most 9 adjacent CH_2 as chain members, it being possible for the bridge member additionally to contain, in any desired sequence, 1 to 4 identical or different chain members selected from O, S, SO_2, CO, CS, NR^5, $C(R^6)_2$, $CR^6=CR^6$, C≡C, CH=N, phenylene, naphthylene, pyridylene and cycloalkylene or cycloalkenylene with in each case 3 to 7 carbon atoms, piperazinylene, piperidinylene, pyrrolidinylene and morpholinylene, wherein R^5 represents a hydrogen atom, a benzyl radical or an alkyl radical with 1 to 4 carbon atoms and R^6 represents a hydrogen atom, a benzyl or phenyl radical, a fluorine or chlorine atom, an alkyl radical with 1 to 4 carbon atoms, a hydroxyl, trifluoromethyl, cyano, carboxyl or amino radical, an alkylamino radical with 1 to 4 carbon atoms in the alkyl radical or a carbalkoxy radical with 1 to 4 carbon atoms in the alkoxy radical, which process comprises:

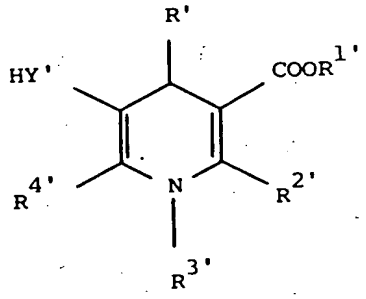
(a) reacting a hydroxy-1,4-dihydropyridine derivative of the general

formula



II

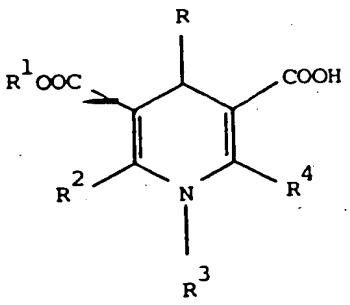
in which R, R^1, R^2, R^3, R^4, Y and X have the definitions given above, with an equivalent amount of a dihydropyridine-3-carboxylic acid derivative of the general formula



III

in which R', $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ and Y' have the definitions given above, but Y' does not represent a carbonyl group, in an inert organic solvent in the presence of water-binding agents at a temperature between 0°C and 180°C, water being split off, or

(b) reacting a 1,4-dihydropyridinecarboxylic acid of the general formula



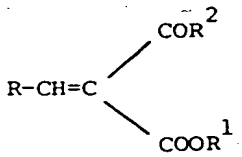
IV

in which R, R^1, R^2, R^3 and R^4 have the definitions given above, is reacted with a bifunctional compound of the general formula

$$Z\text{-}X\text{-}Z' \qquad V$$

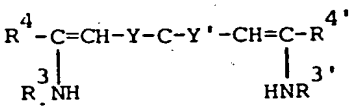
in which X has the definition given above and Z and Z' are in each case identical or different and represent a hydroxyl, mercapto or NHR^5 radical, wherein R^5 has the definition given above, in a molar ratio of about 2:1 in the presence of an inert organic solvent at a temperature between 0°C and 180°C, only a compound of the general formula I in which Y and Y' do not represent a carbonyl group being obtained by this variant, or

(c) reacting an ylidene-β-keto ester of the general formula



VI

R, R^1 and R^2 have the definitions given above, with an enaminocarboxylic acid ester of the general formula



VII

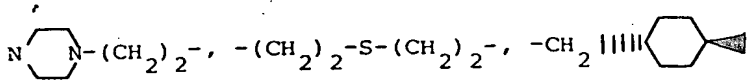
in which R^3, $R^{3'}$, R^4, $R^{4'}$, Y and Y' have the same meanings as defined above, in a molar ratio of about 2:1 in the presence of an inert organic solvent at a temperature between 0°C and 180°C, and, if required, converting a compound of formula I into a pharmaceutically acceptable salt thereof.

2. A process according to claim 1, in which R and R' are identical or different and each represent a phenyl radical or a thienyl, furyl, naphthyl, or pyridyl radical, the phenyl radical optionally being substituted by one or two identical or different substituents selected from nitro, cyano, azido, halogen, trifluoromethyl, hydroxyl, amino and alkyl, alkoxy, alkylamino and alkylmercapto with in each case 1 or 2 carbon atoms in the alkyl groups; R^1 and $R^{1'}$ are identical or different and each represent a straight-chain or branched

B

hydrocarbon radical which has up to 6 carbon atoms and is optionally interrupted in the chain by an oxygen and is optionally substituted by fluorine, chlorine, hydroxyl, phenyl or phenoxy; R^2, $R^{2'}$, R^4 and $R^{4'}$ are identical or different and each represent a hydrogen atom or a straight-chain or branched alkyl radical which has up to 4 carbon atoms and is optionally substituted by fluorine, chlorine, hydroxyl, phenyl or amino; R^3 and $R^{3'}$ are identical or different and each represents a hydrogen atom, an alkyl radical with 1 to 4 carbon atoms or a phenyl, benzyl or phenethyl radical which is optionally substituted by hydroxyl, fluorine or chlorine; Y and Y' are in each case identical or different and denote -COO-, -CONH-, -CO- or $-SO_2-$ and X represents a bridge member which has at least one CH_2 group which is not bonded to the rings and at most 9 adjacent CH_2 groups as chain members, it being possible for the bridge member additionally to contain, in any desired sequence, 1 to 3 identical or different chain members selected from O, S, CO, CS, NR^5, $C(R^6)_2$, CH=N, phenylene, naphthylene, pyridylene, cycloalkylene with 5 to 7 carbon atoms, piperazinylene, piperidinylene, pyrrolidinylene and morpholinylene, wherein R^5 represents a hydrogen atom, a benzyl radical or an alkyl radical with 1 to 4 carbon atoms, and R^6 represents a hydrogen atom, a benzyl or phenyl radical, a fluorine or chlorine atom, or an alkyl radical with 1 to 4 carbon atoms or a hydroxyl, trifluoromethyl, cyano, carboxyl or amino radical.

3. A process according to claim 1 wherein R^3 and $R^{3'}$ are hydrogen, R^2, R^4, $R^{2'}$ and $R^{4'}$ are methyl, R and R' are selected from 3-nitrophenyl, 2-chlorophenyl, 2-nitrophenyl, 2-trifluoromethylphenyl, 2-cyanophenyl, 2-chloro-5-nitrophenyl and 4-naphthyl; R^1 and $R^{1'}$ are selected from methyl, ethyl, isopropyl, methoxyethyl and acetyl; Y and Y' are selected from -COO- and -CONH-, and X is selected from $(CH_2)_n$, wherein n is an integer from 3 to 8, $-(CH_2CH_2O)_2-CH_2CH_2-$, $-(CH_2)_2-O-C_6H_4-O-(CH_2)_2-$, $-(CH_2CH_2O)_3-CH_2CH_2-(CH_2)_2-$



$-(CH_2)_2-NHCONH(CH_2)_2-$ and $-(CH_2)_2-S-S-(CH_2)_2-$.

4. A process according to claim 3 wherein Y and Y' are both -COO- and R and R' are the same and R^1 and $R^{1'}$ are the same.

5. A process according to claim 1(b), in which the reaction is carried out in the presence of a water-binding agent.

6. A process according to claim 1(c), in which the reaction is carried out in an aprotic organic solvent or in an alcohol.

7. A process according to claim 1(a), 1(b) or 5, in which the reaction is carried out in an aprotic organic solvent.

8. A process according to claim 1, 5 or 6, in which the reaction is carried out at a temperature between 20° and 120°C.

9. A compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof, when prepared by a process according to claim 1 or an obvious chemical equivalent thereof.

10. A process according to claim 2 wherein R and R' are both 3-nitrophenyl, R^1 and $R^{1'}$ are both methyl, R^2, R^4, $R^{2'}$ and $R^{4'}$ are all methyl, R^3 and $R^{3'}$ are both hydrogen, Y and Y' are both $-\overset{\overset{O}{\|}}{C}-O-$ and X is $-(CH_2)_6-$.

11. A process for preparing hexanediyl 1,6-bis-[2,6-dimethyl-5-methoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate] which comprises reacting 2,6-dimethyl-5-methoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid with hexane-1,6-diol, in a molar ratio of about 2:1 and in dimethylformamide.

12. The compound hexanediyl 1,6-bis-[2,6-dimethyl-5-methoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate] when prepared by a process according to claim 11 or an obvious chemical equivalent thereof.

13. A process according to claim 1 wherein R and R' are both 2-nitrophenyl, R^1 and $R^{1'}$ are both methyl, R^2, R^4, $R^{2'}$ and $R^{4'}$ are all methyl, R^3 and $R^{3'}$ are both hydrogen, Y and Y' are both $-\overset{O}{\overset{\|}{C}}-O-$ and X is $-(CH_2)_6-$.

14. A process for preparing hexanediyl 1,6-bis-[2,6-dimethyl-5-methoxycarbonyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylate] which comprises reacting hexanediyl 1,6-bis-(3-aminocrotonate) with 2-nitrobenzylideneacetoacetic acid methyl ester, in a molar ratio of about 1:2 in absolute ethanol under nitrogen.

15. The compound hexanediyl 1,6-bis-[2,6-dimethyl-5-methoxycarbonyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylate] when prepared by a process according to claim 14 or an obvious chemical equivalent thereof.

16. A process according to claim 1 wherein R and R' are both 3-nitrophenyl, R^1 and $R^{1'}$ are both 2-methoxyethyl, R^2, R^4, $R^{2'}$ and $R^{4'}$ are all methyl, R^3 and $R^{3'}$ are both hydrogen, Y and Y' are both $-\overset{O}{\overset{\|}{C}}-O-$ and X is $-(CH_2)_6-$.

17. A process for preparing hexanediyl 1,6-bis-[2,6-dimethyl-5-(2-methoxy)-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate] which comprises reacting [illegible]hexanediyl 1,6-bis-(3-[illegible]crotonate) with [illegible]nzylidene-acetoacetic acid 2-methoxy ethyl ester in a molar ratio of about 1:2 in absolute alcohol under nitrogen.

18. The compound hexanediyl 1,6-bis-[2,6-dimethyl-5-(2-methoxy)-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate] when prepared by

a process according to claim 17 or an obvious chemical equivalent thereof.

19. A process according to claim 1 wherein R and R' are both 2-chlorophenyl, R^1 and $R^{1'}$ are both methyl, R^2, R^4, $R^{2'}$ and $R^{4'}$ are all methyl, R^3 and $R^{3'}$ are both hydrogen, Y and Y' are both $-\overset{\overset{O}{\|}}{C}-O-$ and X is $-(CH_2)_8-$.

20. A process for preparing octanediyl 1,8-bis-[2,6-dimethyl-5-methoxycarbonyl-4-(2-chlorophenyl)-1,4-dihydropyridine-3-carboxylate] which comprises reacting hexanediyl 1,6-bis-(3-aminocrotonate) with 2-chlorobenzylideneacetoacetic acid methyl ester in a molar ratio of about 1:2 in absolute ethanol under nitrogen.

21. The compound octanediyl 1,8-bis-[2,6-dimethyl-5-methoxycarbonyl-4-(2-chlorophenyl)-1,4-dihydropyridine-3-carboxylate] when prepared by a process according to claim 20 or an obvious chemical equivalent thereof.

22. A process according to claim 1 wherein R and R' are both 3-trifluoromethylphenyl, R^1 and $R^{1'}$ are both ethyl, R^2, R^4, $R^{2'}$ and $R^{4'}$ are all methyl, R^3 and $R^{3'}$ are both hydrogen, Y and Y' are both $-\overset{\overset{O}{\|}}{C}-O-$ and X is $-(CH_2)_2-S-(CH_2)_2-$.

23. A process for preparing bis-(2-hydroxyethyl)-sulphide bis-[2,6-dimethyl-5-ethoxycarbonyl-4-(2-trifluoromethylphenyl)-1,4-dihydropyridine-3-carboxylate] which comprises reacting bis-(2-hydroxyethyl)-sulphide bis-(3-aminocrotonate) with 2-trifluoromethylbenzylideneacetoacetic acid ethyl ester in a molar ratio of 2:1 in absolute ethanol under nitrogen.

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24. The compound bis-(2-hydroxyethyl)-sulphide bis-[2,6-dimethyl-5-ethoxycarbonyl-4-(2-trifluoromethylphenyl)-1,4-dihydropyridine-3-carboxylate] when prepared by a process according to claim 23 or an obvious chemical equivalent thereof.

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